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Title: Genome-wide prediction of childhood asthma and related phenotypes in a longitudinal birth cohort

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Body: Aim: Childhood asthma varies greatly in clinical presentation and time course and underlying disease pathways are assumed to be heterogenous. We assessed the extent to which single nucleotide polymorphisms (SNPs) associated with childhood asthma in a genome-wide association study (GWAS) are predictive of asthma-related phenotypes. Method: In 8365 children from a population based birth cohort, the Avon Longitudinal Study of Parents and Children, allelic scores were derived based on between 10 and 215443 SNPs ranked according to inverse of the p-value for association with physician diagnosed asthma in an independent GWAS (6176 cases and 7111 controls). We assessed the predictive value of allelic scores for asthma-related outcomes at age 7-9 years (physician's diagnosis, early wheezing phenotypes, pulmonary function, bronchial hyper-responsiveness (BHR) and atopy). Results: Scores based on the 46 highest-ranked SNPs were associated with persistent ($P<10^{-11}$, area under ROC curve (AUC)=0.59) and intermediate onset ($P<10^{-3}$, AUC=0.58) wheeze. Among lower-ranked SNPs (ranks 21545-46416), there was evidence for associations with diagnosed asthma ($P<10^{-4}$, AUC=0.54) and atopy ($P<10^{-5}$, AUC=0.55). We found little evidence of associations with transient early wheezing, reduced pulmonary function or non-asthma phenotypes. Conclusion: The genetic origins of asthma are diverse: some pathways are specific to wheezing syndromes while others are shared with atopy and BHR. Our study also provides evidence of aetiological differences among wheezing syndromes. Funding: BDS is recipient of a ERS/Marie Curie Joint Research Fellowship (MC 1614-2010); RG was supported by the UK Medical Research Council (0401540).